Attorney Docket No. 62605-11

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Division Under 37 C.F.R. 1.53(b)
Application of: Lee et al.

Prior Application Serial No.: 08/951,873

Prior Filing Date: October 17, 1997

Prior Group Art Unit: 1614

Anticipated Classification of this Application:
Class 514 Subclass 243.000

Examiner: J. Goldberg

For: **1,2,4-BENZOTRIAZINE OXIDES AS RADIOSENSITIZERS AND SELECTIVE CYTOTOXIC AGENTS**

CERTIFICATE UNDER 37 C.F.R. 1.10

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I hereby certify that this paper is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" Service on the date indicated above and is addressed to: Commissioner for Patents, Box Patent Application, Washington, DC 20231

Geraldine D. Shea

Signature

Commissioner for Patents
Box Patent Application
Washington, D.C. 20231

Dear Sir:

CITATION OF REFERENCES

Enclosed herewith is an Information Disclosure Statement by Applicant, which cites a number of references for consideration by the Examiner.

This Information Disclosure Statement is being filed concurrently with the above-identified application and, consequently, no fee or statement pursuant to 37 C.F.R. §1.97(c) or (d) is required. Furthermore, pursuant to 37 C.F.R. §1.98(d), copies of the cited references are not being provided as they were previously cited by or submitted to the Examiner in prior application Serial No. 07/409,480, filed September 18, 1989, which is relied upon for an earlier filing date under 35 U.S.C. §120.

Respectfully submitted,

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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:
WILLIAM W. LEE et al.
Serial No.: 07/409,480 Group Art Unit: 223
Filed: 18 September 1989 Examiner: Unknown
For: 1,2,4-BENZOTRIAZINE OXIDES AS RADIOSENSITIZERS AND SELECTIVE CYTOTOXIC AGENTS

INFORMATION DISCLOSURE STATEMENT
UNDER 37 C.F.R. §1.97

The Honorable Commissioner of
Patents and Trademarks
Washington, D.C. 20231

Sir:

The following information may be material to the examination of the above-identified application and is, therefore, submitted in compliance with applicants' duty of disclosure as defined in 37 C.F.R. §1.56. The Examiner is requested to make these citations of official record in the application.

U.S. Patents

U.S. Patent No. 2,489,352 to Wolf et al. discloses substituted 1,2,4-benzotriazine oxides, wherein, according to applicants' structural formula (e.g., as drawn in claim 1), X is NH_2, n is 0 and Y^1 and Y^2 are independently either H, halogeno or hydrocarbyl. The only

recited use of the compounds is in the treatment of malaria.

U.S. Patent No. 2,489,359 to Wolf et al. discloses substituted 1,2,4-benzotriazine oxides wherein, according to applicants' structural formula, X is NHR or NR_2 where R is alkyl (1-4C), Y^1 is hydrogen, Y^2 is 7-halogeno, and n is 0.

U.S. Patent No. 3,079,390 to Jiu et al. discloses substituted 1,2,4-benzotriazine oxides, wherein, according to applicants' formula, X is NHR or NR_2, n is 0, Y^1 and Y^2 are hydrogen, and R is morpholino, -NH-(CS)-NH_2, or hydroxy-substituted alkyl. The compounds are stated to be useful as antiinflammatory agents.

U.S. Patent No. 3,482,024 to Molnar et al. describes substituted 1,2,4-benzotriazine oxides stated to be useful starting materials in the preparation of 1,2-dihydro-1,2,4-benzotriazine derivatives. According to applicants' structural formula, the disclosed 1,2,4-benzotriazine oxide intermediates are wherein X is lower alkyl, aryl, free or substituted amino, or free, alkylated or acylated hydroxyl groups, n is 0, and Y^1 and Y^2 are H, halogen, lower alkyl, free and substituted amino groups and free, alkylated or acylated hydroxyl groups.

U.S. Patent No. 3,868,371 to Ley et al., cited in the specification at page 4, describes substituted 1,2,4-benzotriazine oxides as antimicrobial agents. Using applicants' structural formula, X is NH_2, n is 1, and Y^1 and Y^2 are selected from a variety of substituents, including hydrogen, halogen, lower alkyl, halo(lower alkyl), lower alkoxy, carbamyl, sulfonamido, carboxy or carbo(lower alkoxy).

U.S. Patent No. 3,957,779 to Seng et al., cited in the specification at page 4, discloses, as antibacterial

compounds, 1,2,4-benzotriazine-1,4-di-N-oxides that have a substituted amino group in the 3-position. Also disclosed as starting materials are the 3-NH_2 (unsubstituted amino) analogs of these compounds, including those wherein Y^1 and Y^2 are both hydrogen.

U.S. Patent No. 3,980,779 to Ley et al., cited in the specification at page 4, is a divisional of U.S. Patent No. 3,868,371, cited supra.

U.S. Patent No. 3,991,189 to Seng et al., cited in the specification at page 4, discloses 1,2,4-benzotriazine oxides wherein, according to applicants' formula, X is NH_2, n is 1 and Y^1 and Y^2 are hydrogen, alkyl, alkoxy, halo(alkyl) or halogen. Also disclosed are compounds wherein n is 1 and X is NHR where R is alkyl, alkenyl, etc. The 3-NH_2 compounds are stated to be useful as intermediates in the preparation of the 3-NHR compounds, while the stated utility of the 3-NHR compounds is in inhibiting growth of bacteria, fungi or yeast.

U.S. Patent No. 4,001,410 to Ley et al., cited in the specification at page 4, discloses 1,2,4-benzotriazine-1,4-di-N-oxides having an unsubstituted amino group at the 3-position (i.e., as "X"). As in U.S. Patent No. 3,868,371, the parent of this case, one of Y^1 and Y^2 is hydrogen, halogen, lower alkyl, halo(lower alkyl), lower alkoxy, carbamyl, sulfonamido, carboxy or carbo(lower alkoxy), and the other is halogeno, lower alkyl, halo(lower alkyl), lower alkoxy, carbamyl, sulfonamido, carboxy or carbo(lower alkoxy). The compounds are stated to be useful as antibacterials and as growth promotants for livestock.

U.S. Patent No. 4,027,022 to Seng et al. is a divisional of U.S. Patent No. 3,957,779, discussed above.

U.S. Patent No. 4,067,981 to Sasse et al. discloses, at col. 2, a 1,2,4-benzotriazine-3-ether 1-oxide, i.e., wherein one of Y^1 and Y^2, according to applicants' structural formula, is hydrogen, and the other is halogen, trifluoromethyl or alkoxy, X is -OR wherein R is alkyl (1-8C) optionally substituted with halogen, lower alkoxy or alkenyl (3-6C), and n is 0. The compounds are stated to possess fungicidal, bactericidal, insecticidal and acaricidal properties.

U.S. Patent No. 4,091,098 to Lumma, Jr. describes 1,2,4-benzotriazine oxides as anorectic, antidepressant, analgesic and hypnotic agents. The disclosed compounds, according to applicants' structural formula, are those wherein X is a morpholino moiety, n is 0, and one of Y^1 and Y^2 is hydrogen while the other is halogen, trifluoromethyl, lower alkyl, lower alkylthio, lower alkoxy, or hydrogen.

U.S. Patent No. 4,160,833 to Diel describes 1,2,4-benzotriazine-1,4-di-N-oxide derivatives having an amide moiety or an $-N=C(R)-NR_2$ group at the 3- ("X") position. The compounds are stated to be useful for the control of microorganism, as animal feed additives, and for the "protection of materials".

U.S. Patent No. 4,206,212 to Sasse et al. discloses, as a starting material to make a 3-halogeno-1,2,4-benzotriazine-1-oxide (i.e., wherein "X" is halogen), compounds according to applicants' structural formula wherein n is 0, X is NH_2 or OH, and Y^1 and Y^2 are halogen, nitro, alkyl, halo(alkyl), alkoxy, alkylmercapto or alkylsulfonyl, phenoxy, or a phenylmercapto radical (at col. 4).

U.S. Patent No. 4,247,691 to Diel describes 1,2,4-benzotriazine-di-N-oxide derivatives having a 3-amide moiety, i.e., at applicants' "X" position.

U.S. Patent No. 4,289,771 to Sasse et al. describes 1,2,4-benzotriazine-1-oxides having a 3-sulfonyl moiety, i.e., at applicants' "X" position.

U.S. Patent No. 4,316,022 to Hajos et al. benzo-as-triazine derivatives, compounds which are structurally related to 1,2,4-benzotriazines.

Foreign Patent Documents

WO 88/02366 (published 7 April 1988) is the publication of the PCT application corresponding to great-grandparent case Serial No. 06/911,906.

Publications

R.H. Atallah et al., Tetrahedron 38(12):1793-1796 (1982), describe 3-methyl-1,2,4-benzotriazine-1-oxide and -1,4-dioxide (i.e., according to applicants' formula, X is methyl, Y^1 and Y^2 are H, and n is 0 or 1).

*M.A. Baker et al., Cancer Research 48:5947-5952 (1988), describe applicants' compound "SR4233" (i.e., the substituted 1,2,4-benzotriazine wherein, according to applicants' formula, X is NH_2, Y^1 and Y^2 are H, and n is 1) as a selective cytotoxic agent.

*K.R. Laderoute et al., Biochemical Pharmacology 35(19):3417-3420 (1986) also describe SR4233 as a selective cytotoxic agent.

*K. Laderoute et al., Biochemical Pharmacology 37(8):1487-1495 (1988) present a study of the molecular mechanism involved in the selective cytotoxicity of SR4233.

J.C. Mason et al., J. Chem. Soc. (B) 5:911-916 (1970) disclose a number of substituted 1,2,4-benzotriazine oxides. The compounds disclosed which are relevant to applicants' claims are at page 915 wherein, according to applicants' formula, X is NH_2, n

is 0 or 1, and Y^1 and Y^2 are hydrogen, methyl, methoxy or chloro.

F. Seng et al., Angew. Chem. internat. Edit. 11(11):1009-1010 (1972), disclose 1,2,4-benzotriazine oxides wherein, according to applicants' formula, X is NH_2, n is 1, and Y^1 and Y^2 are H.

*M.I. Walton et al., J. Chromatogr. 430(2):429-437 (1988), present a study of the enzymology, pharmacokinetics and metabolism of SR4233 (i.e., wherein X is NH_2, n is 1, and Y^1 and Y^2 are H) as a selective cytotoxic agent.

*E.M. Zeman et al., Int. J. Radiation Oncology Biol. Phys. 12:1239-1242 (1986), describe SR4233 as useful in selectively killing hypoxic cells.

*E.M. Zeman et al., Radiotherapy and Oncology 12:209-218 (1988) present further studies on the enhancement of radiation-induced cell killing by SR4233. On page 217, the authors state that the paper was presented in part at a conference held September 28-October 1, 1986.

None of the references summarized above -- with the possible exception of one or more of those references marked with an asterisk -- disclose (1) the claimed method of using certain 1,2,4-benzotriazine oxides as selective cytotoxic agents, (2) the claimed method of using certain 1,2,4-benzotriazine oxides as radiosensitizers, or (3) the claimed 1,2,4-benzotriazine oxides themselves.

For purposes of applicability of the references, the effective filing dates of applicants' claims are as follows. Four applications in this family of applications have now been filed: U.S. Serial No. 06/911,906,

filed 25 September 1986; U.S. Serial No. 07/169,873, filed 18 March 1988, a continuation-in-part of the '906 application; Serial No. 07/356,602, a file wrapper continuation of the '873 application, filed 24 May 1989; and the present application, a continuation-in-part of the '602 application. The subject matter of claims 3, 17, 32, 54, 56-59 and 62-63 is fully supported by and thus entitled to the filing date of the '906 application, 25 September 1986. Claims 11-12, 26-27, 44-45, 55, 60-61 and 64-65, i.e., wherein X is H or hydrocarbyl (1-4C), are entitled to a filing date at least as early as that of second application Serial No. 07/169,873, 18 March 1988. The remaining claims are entitled to a filing date at least as early as that of the present application.

Applicants also call attention to the accompanying Declaration Under 37 C.F.R. §1.131 filed in the parent case. In that Declaration, Dr. J. Martin Brown, one of the inventors of the subject matter of claims 3-6, 13-20 and 27-35 of that application, avers that the claimed methods and compounds were conceived and reduced to practice prior to October, 1985, and thus prior to the effective dates of the references asterisked above. The references so marked, similarly, are not available as prior art against claims 3, 17, 32, 54, 56-59 and 62-63 herein, i.e., claims which are entitled to the filing date of great-grandparent application Serial No. 911,906.

This Information Disclosure Statement under 37 C.F.R. §1.97 is not to be construed as a representation that a search has been made, that additional information

material to the examination of the application does not exist, or that any one or more of these citations constitutes prior art under 35 U.S.C. §102.

Respectfully submitted,
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